

Risk Factors of mortality among French Canadian children during the measles epidemic of 1714-15

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Introduction

In past populations, measles epidemics were responsible for many deaths, especially among young children. An example of one such crisis was in New France. During the 2nd quarter of 1714 (around March), there was a sudden increase in mortality in the Western part of the colony. By the 3rd quarter (around September), the epidemic had spread to all parts of the colony and had run its course by the second quarter of 1715 (Mazan et al., 2009). It was found that the epidemic was quite fatal among all children under 15 years of age, but severity declined with age and varied by sex and region. It was estimated that children in the East had the highest risk of death in the colony and females were more likely than males to have died from the virus. As such, the severity of the epidemic was probably a combination of more severe malnutrition in the East and sibling transmission in the household. Together, these factors may have made the inhabitants highly vulnerable and probably contributed to the high severity of the measles epidemic.

Pre-existing malnutrition is regarded as a major risk factor of death from measles (Clements and Hussey, 2004; Moss and Ota, 2007). For instance, increased measles mortality has been associated with increases in wheat prices (a proxy for malnutrition) during the 17th and 18th centuries in England (Duncan et al. 1997). It is believed that the influence of malnutrition is probably mediated through immune suppression (Clements and Hussey, 2004). In particular, protein energy malnutrition and Vitamin A deficiency have been linked to an increased risk of death from measles. Arguably, an improved diet and Vitamin A supplementation during an epidemic leads to a 'marked fall' in measles mortality (Barclay et al., 1987; Berman, 1991; Clements and Hussy, 2004).

On the other hand, several community studies in Guinea-Bissau, Senegal, Gambia, Bangladesh, United Kingdom and Denmark found that mortality was higher in families with several cases and among secondary cases (i.e. children infected at home). In these studies, the effect of malnutrition was believed to be less important than overcrowding (i.e. number of persons per room and members in the household) and intensive exposure to the virus (Garenne and Aaby, 1989; Aaby, 1984; 1988, Pison et al., 1992). It was posited that overcrowding or close contact with other family members increases the intensity of exposure to the virus in the household and in turn, increases the risk of acute measles death. This implies that the effect of crowding and clustering on the risk of death may be mediated through intensive exposure to the virus. The increased mortality risk associated with the close contact of family members is usually explained as a dose-response effect: the closer the contact between family members, the higher the dose of infective particles transmitted and the higher the mortality of other family members. As such, close physical contact between family members implies the absorption of larger and more lethal dose of the virus (Aaby, 1988).

In all of the above studies, the age at infection has consistently been found to be an important risk factor of measles mortality. The risk of acute measles death tends to peak between 6 and 24 months of age (Burstrom et al., 1999). Typically, younger children have an underdeveloped immune system and this makes them at a higher risk of dying from measles. Because of the high risk during childhood, it is believed that large families with many young children are at an increased risk of infection at younger ages. This is probably why children with siblings tend to have a higher risk of death than single child families. This pattern suggests that the age

composition of the children in the family may also be an important risk factor during early childhood. Pison et al., (1992) found that a larger age difference between sibling pairs resulted in a higher odds of death from measles. Older children or the parents are probably more likely to introduce measles into the household through outside contacts (index cases). In turn, younger children who are infected (secondary cases) are believed to receive a more lethal dose and given the age-associated differences in risk, they have a greater likelihood of dying (Reves, 1985; Hull, 1988; Koster, 1988; Pison et al., 1992; Burstrom et al., 1999).

Historical data from Quebec provides a suitable context to test some of the above assumptions on the risk factors of measles deaths during an epidemic. Social and environmental conditions were mostly homogeneous and benefited the majority of inhabitants. A typical family had a large number of young children living in the household and thus, a highly susceptible host population. Further, as this was the first known measles epidemic, no prior exposure would put the entire colony at a great disadvantage, as the Canadian born probably had no acquired immunity to the virus. This also means that there were enough deaths to generate more reliable estimates of the risk factors than in most of the above community studies. Most of those studies were based on a small number of subjects, making the reliability of their estimates uncertain at times.

A problem with the Quebec data is that parish clergy did not record the cause of death at the time, so we don't know who exactly died from measles during the epidemic. However, we have a good estimate of the duration of the epidemic and judging by the consistent patterns found in the above studies, measles tends to have a highly predictable outcome. Thus, a crude way to try and disentangle the risk factors of the measles epidemic when cause of death information lacking is to compare models applied during the epidemic period with the same models applied to mortality under normal conditions (i.e. a form of validation). Taking these issues into consideration, this study seeks to explore the effects that the above risk factors had on the children under 5 years of age during the epidemic of 1714-15. Using GEE binary logistic regression models to account for correlated responses, I examine the likelihood of death of these children by such risk factors as the age at infection, size, sex and age differences of the children in the household. As the risk of death also varied across the colony, I included an additional proxy to capture spatial trends in mortality during that time.

Data and Methods

The data used in this study originates from the highly reliable and accurate *Registre de population du Québec ancien*, compiled by the *Programme de recherche en démographie historique* (PRDH) at the Université de Montréal (Légaré 1988; Charbonneau et al. 1993). The database contains, for individuals that lived in the Saint-Lawrence Valley in the 17th and 18th centuries, the date and place of birth, death and marriage(s), names of parents and spouse(s) and secondary information on places of residence and of origin. The population remained quasi-closed until the 19th century because of particular historical and geographical circumstances, and thus the usual problem of missing observations due to migration is greatly reduced (Charbonneau et al. 1993; Desjardins 1996). As the development of the database is still in progress, the available information varies in time according to the date of the events and the period of birth and marriage of the individuals. Births are matched with individuals and their parents up to 1776,

and deaths up to around 1850 (relating to individuals born before 1750). All ancestors of every individual who married before 1800 can be traced back to the founders of the population.

Study Population

The selection of the study population was based on several criteria. As mentioned above, one drawback of the Quebec data is that parish priests did not record the cause of death during those times. As such, we don't know exactly who was infected and died from the measles virus. This makes it difficult to distinguish between the effects of measles and all other causes of death. However, measles typically follows a predictable seasonal pattern and usually peaks in late winter/early spring and autumn. In addition, we have an accurate estimate of the temporal and spatial patterns of the epidemic. In a previous study, we found that the epidemic began during the 2nd quarter of 1714 in the Western parishes and had run its course by the 2nd quarter of 1715 (Mazan et al., 2009). This prior information helps provide the foundation for the study group.

One method to analyze risk factors during the epidemic when the cause of deaths is unknown is to maximize the chance of selecting individuals who were exposed to the virus. To achieve this, I imposed several criteria to select the study group. Most of the selection criteria are based on findings from the previous demographic study. Although the epidemic was of a longer duration, I only selected children who died during the 3rd and 4th quarters of 1714. The epidemic peaked during this time (in the East) and it is more likely that any deaths were acute measles fatalities. Only children under 5 years of age were selected for this study because they had much higher than average mortality during this period and most deaths occurred at these ages. In addition, younger children are usually at the highest risk of dying from measles. Neo-natal infants and deaths were excluded, as it has been found that these rates are subject to a high degree of random variation over time and they appeared to be more resistant to death from measles in our population based study.

Third, I only selected families with Canadian born children, as many immigrant sibships could not be linked together. Many of these mothers did not have an identification number to allow linkage of the family members. Lastly, I focus on children who resided in well-established parishes at the time of the epidemic. In the last study, we examined 63 established parishes over the course of the epidemic. In this study, I narrow the focus to fewer parishes. In particular, I selected parishes that had death rates well above expected mortality under normal conditions. A larger than normal level of mortality probably indicates that many of the excess deaths may have been due to the measles virus. There were 25 parishes that fit this criterion and selected for the study¹.

¹ To determine where a child was living during the epidemic is not straightforward because only information on the parish of birth, marriage and death is available. Internal migration was quite common in the colony and if the transient population was not taken into consideration, estimates could be significantly biased. One method to lessen the potential bias introduced by internal migration is to estimate the region of residence for each individual at any given time by using information about other family members. I used the following criteria: 1) If all family members were born and died in the same parish, this was used as the place of residence for each member; 2) When the parish of birth and death were different for some members and there was a birth or death in the family during the year of interest, we used the recorded parish of the event as the place of residence for the entire family and; 3) Otherwise, the parish with the most recent birth or death prior to the year of interest was designated as the current residence of that particular family.

As such, the study population consists of Canadian born children between the ages of 1 and 60 months who were alive at some point in the established parishes during the 3rd and 4th quarters of 1714 (n = 2,651). To help disentangle some of the differences in mortality risk from other causes, I also used the same criteria to select a group of individuals living through periods with no known epidemic, as a basis for comparison. The selection criteria of the normal periods were the same with one exception. The comparison groups were observed over a 3 year period (i.e. 1708-10, n = 2,870 and 1721-23, n = 3,402). A longer period of observation was necessary to obtain an adequate number of deaths in order to form a reliable basis of comparison.

Risk Factors

For the study, I incorporate a model with two main components. The first component consists of demographic risk factors. The region of residence at the time of the epidemic was included to capture the regional (urban/rural) differences in mortality. During the epidemic period, this measure also serves as a proxy for malnutrition, as the East was believed to be disadvantaged in terms of this attribute and suffered a greater number of losses than the West. Quebec City and Montreal are presented as their own separate regions or as the major urban centers. Otherwise, the remaining 23 rural parishes were divided into 3 broad regions, Rural West, Greater Quebec Area (GQA) and Rural East. The Rural West serves as the reference category. The risk of death from measles has a largely predictable age pattern. Typically, measles mortality tends to peak between the ages of 6 and 24 months and declines thereafter (Burstrom et al., 1999). The age at the time of the epidemic was divided into 4 groups to reflect this pattern: <6 months, 6 to 11 months, 12 to 23 months and 24+ months. Individuals who were 24 months and older served as the reference category. The sex of the child was also included as a risk factor of childhood mortality death from measles. Generally, females have been found to have a lower probability of survival during and epidemic (Garenne, 1994). Males serve as the reference category.

The immigrant status of the parents has not been included as a risk factor in any of the above studies. External migration is probably not an important issue in those countries where the studies took place. However, in New France there were a considerable number of immigrants at any given time. Immigrant status was included in the models because it is possible that immigrant parents, especially fathers and both parents may have lacked support from extended kinship during crises such as, 'poor harvests'. Large well established Canadian families may have acted as a buffer against crises such as food shortages by helping one another (i.e. access to abundant resources), while immigrant parents may have had little aid in a time of crisis. Immigrant status of parents was categorized into 4 groups to explore this assumption: Canadian born parents, Mother, Father and Both Parents. Canadian born parents serve as the reference category.

The second component of the model consists of characteristics of the children and their siblings. The number of children in the household is an important risk factor of measles death. This factor usually serves as a proxy for overcrowding and the intensity of exposure to the virus. Generally, one would expect that families with numerous younger children would be at higher probability of

death. A larger number of siblings can increase the transmission rate and intensity or it could reflect material deprivation in contemporary populations (Burstrom et al., 1999). The number of siblings in the household includes all unmarried siblings in a given period, with the exception of neonates. Number of siblings was coded in some models as: 1 or 2 siblings and 3 or more siblings, with 3+ children serving as the reference group. In other models it is coded as: No siblings, 1 or 2 siblings and 3 or more siblings.

Another factor not taken into consideration in other studies is the death of a sibling during the epidemic period. The death of a sibling may reflect the incidence of multiple and secondary cases in a given family. This may especially be a good alternative when that type of information is lacking, as in this study. It is important to know about secondary cases because they have been found to be at the highest risk of death during an epidemic (i.e. the dose response effect). If there is a death in the family, then it could be an indication of multiple cases in the household. In turn, generational intensity of the virus may increase the risk of death for the other siblings (Aaby, 1988). No dead siblings during the given period served as the reference group.

The age difference from the sibship is also included in the models. As mentioned above, it has been found that older siblings (index cases) may increase the risk of measles death among their younger siblings (secondary cases) by introducing the virus into the household. This factor was estimated by subtracting each child's age at time x from the average age of the sibship at time x . The average age difference was then coded as < 2 years, 2 to 5 years and 6+ years; with < 2 years serving as the reference group. As well, in some models, same and opposite sibling pairs were examined to check if cross-sex transmission increased the risk of death. Pison et al. (1992) and Aaby (1992) found that siblings of the opposite sex were at a higher risk of dying. Same sex sibling pairs serve as the reference group. Table 1 summarizes the coding of the covariates and gives the number of families in each category for the GEE logistic regression models.

Table 1. – Description of the categorical variables included in the GEE logistic regression models.

Risk Factor	Model A	Model B	Model C
	Normal (1708-10) n _{GEE} = 2,870	Epidemic (1714) n _{GEE} = 2,651	Normal (1721-23) n _{GEE} = 3,402
<u>Region</u>	768	772	774
Rural East	368	300	489
Quebec City	722	632	772
GQA	482	423	562
Montreal	530	524	805
Rural West[†]			
<u>Age</u>			
<6 months	599	398	709
6 to 11 months	248	221	344
12 to 23 months	557	511	605
24+ months[†]	1,466	1,521	1,744
<u>Immigrant Status</u>			
Both Parents	195	123	115
Mother	202	205	271
Father	879	731	770
French Canadian[†]	1,594	1,592	2,246
<u>Sex</u>			
Male	1,361	1,323	1,607
Female[†]	1,509	1,328	1,795
<u>No. of Siblings</u>			
1 or 2 Sibs	1,001	929	1,328
3+ Sibs[†]	1,869	1,722	2,074
<u>Sibling Survival</u>			
Sibling died	472	396	527
None[†]	2,398	2,255	2,875
<u>Age Difference</u>			
6+ years	881	887	962
2 to 5 years	1,213	1,130	1,462
< 2 years[†]	776	634	978

[†] Reference category- basis of comparison for the other categories.

Binary logistic regression models for correlated responses (GEE)

As there can be more than one family member in study group, the data can be highly correlated. If the correlated responses are not taken into consideration, then incorrect inferences may result. To account for correlated responses, I used a GEE binary logistic regression model to assess the effects of the regional and sibling risk factors on the odds of a child dying during the measles epidemic and the normal periods. Generally, the interpretation of GEE coefficients and

significant test are the same as the standard logistic regression. However, the underlying assumptions and the method of estimating the coefficients are different from the standard regression (Kleinbaum and Klein, 2002). The GEE model uses a quasi-likelihood method to estimate the regression coefficients and robust variance estimation to estimate standard errors, which account for the correlated responses. The GEE binary logistic regression takes on the same form as standard logistic regression when given as the logit transformation:

$$\text{logit}(\pi) = \beta_0 + \beta_i X_i + \dots + \beta_j X_j;$$

where β_0 is the intercept of the model, β_i is the slope and X_i is any given value of the independent variable. As π increases from 0 to 1, the odds increases from 0 to ∞ and the logit increases from $-\infty$ to ∞ . For $\beta > 0$, π increases as X increases, while for $\beta < 0$, π decreases as X increases. The main assumption of the model is that children are correlated within clusters, but are independent between clusters. In this analysis, the mother is the ‘between cluster group’, while her children are the ‘within cluster’ group. Unlike standard logistic regression, the GEE model requires that correlation structure must be specified for the estimation of the correlation parameters, coefficients and standard errors. In this study, the correlation structure was assumed to be independent (i.e. responses are uncorrelated within clusters). For regression diagnostics, I checked cross tabulations to search for zero cell counts and complete separation. I also examined deviance and studentized residuals for outlying cases and Cook’s distance for influential cases. No serious problems were found in the data.

Results

Table 2. gives the descriptive statistics of the families with children under 5 years of age living through the peak of the epidemic (3rd and 4th quarters of 1714) and the normal periods (1708-10 and 1721-23). Generally, the means and standard deviations of the study periods are similar to one another. During the epidemic period, there was an average of 4.7 unmarried children (SD = 2.1) living in the household (2.4 girls and 2.3 boys). The average age of the siblings was 6.7 years (SD = 3.7) and the average age difference from the sibship was 4.8 years (SD = 3.2).

Table 2. – Descriptive statistics of families during the measles epidemic of 1714 and the comparison groups of 1708-10 and 1721-23, New France.

Descriptives	Normal (1708-10)		Epidemic (1714)		Normal (1721-23)	
	MEAN	SD	MEAN	SD	MEAN	SD
No. of unmarried children in the household	4.7	2.2	4.7	2.1	4.6	2.3
No. of unmarried boys in the household	2.3	1.5	2.3	1.5	2.2	1.5
No. of unmarried girls in the household	2.5	1.6	2.4	1.5	2.4	1.5
Age of siblings in the household	6.1	3.7	6.7	3.7	5.9	3.9
Age difference from siblings in the household	4.5	3.3	4.8	3.2	4.4	3.3
Age of children under the age of 5 in the household	2.2	1.5	2.4	1.5	2.2	1.6
	N		N		N	
No. of Families (Subject Effect)	1,387		1,414		1,645	
No. of Children under 5 years (Within-Subject Effect)	2,870		2,651		3,402	
No. of Boys under 5 years	1,355		1,323		1,790	
No. of Girls under 5 years	1,504		1,328		1,603	

Table 3 gives the odd ratios (OR_{GEE}) and the robust standard errors (SE) of the GEE logistic regression models (A through C) fit to the data during the 3rd and 4th quarters of 1714 and the comparison models representing normal mortality conditions (1708-10 and 1721-23). In addition, the bootstrap odds ratios (OR_{BS}) are also provided to demonstrate the stability of the parameter estimates and as a check for bias in the models. To obtain the bootstrap coefficients, I randomly selected 1 child from each family with replacement. The random selection procedure was repeated 100 times. Models A through C include all of the risk factors entered simultaneously. For clarity, I don't present the bivariate and nested models. The risk factors remain stable under all those circumstances. All models and especially the epidemic model appear to fit the data reasonably well and the bootstrap odds ratios are in general agreement with the GEE estimated ratios.

Table 3. – GEE and bootstrap logistic regression models of childhood risk factors applied to the measles epidemic of 1714 and the comparison groups of 1708-10 and 1721-23.

Risk Factor	Model A			Model B			Model C		
	Normal (1708-10)			Epidemic (1714)			Normal (1721-23)		
	OR _{GEE}	SE (B)	OR _{BS}	OR _{GEE}	SE (B)	OR _{BS}	OR _{GEE}	SE (B)	OR _{BS}
Region									
Rural East	0.71	0.225	0.76	1.50*	0.203	1.79	0.50**	0.241	0.49
Quebec City	1.79*	0.231	1.93	2.66***	0.224	2.62	1.61*	0.190	1.72
GQA	1.01	0.215	1.03	1.91***	0.199	1.97	0.95	0.180	0.87
Montreal	1.40	0.223	1.50	1.10	0.233	1.20	2.12***	0.168	2.26
Rural West [†]									
Age									
<6 months	5.66***	0.190	6.49	4.21***	0.192	3.91	10.17***	0.175	8.78
6 to 11 months	4.71***	0.238	5.29	3.63***	0.226	3.48	5.25***	0.219	4.61
12 to 23 months	4.01***	0.188	4.74	4.87***	0.167	5.26	3.93***	0.190	3.88
24+ months [†]									
Immigrant Status									
Both Parents	1.04	0.260	1.16	2.26***	0.254	2.70	0.92	0.320	0.74
Mother	1.36	0.232	1.64	0.75	0.268	0.83	0.99	0.239	0.98
Father	1.07	0.157	1.16	1.36*	0.146	1.38	1.17	0.129	1.14
French Canadian [†]									
Sex									
Male	1.43**	0.131	1.33	1.32*	0.127	1.27	1.46**	0.121	1.46
Female [†]									
No. of Siblings									
1 or 2 Sibs	0.75	0.158	0.76	1.80***	0.149	1.79	1.01	0.149	1.24
3+ Sibs [†]									
Sibling Survival									
Sibling died	1.26	0.232	1.34	4.00***	0.211	4.07	1.53*	0.217	1.65
None [†]									
Age Difference									
6+ years	0.63*	0.216	0.60	1.92**	0.222	1.83	0.70	0.211	0.81
2 to 5 years	0.74	0.169	0.72	1.48*	0.185	1.53	0.75	0.153	0.81
< 2 years [†]									

[†] Reference category- basis of comparison for the other categories.
p < .001***, p < .01**, p < .05*

The region of residence was an important childhood risk factor, especially in Models B and C. However, the likelihood of death varied by the time period under consideration. During the epidemic, children residing in the Eastern regions, particularly in Quebec City and the Greater Quebec Area were more likely to have died than ones residing in the Rural West. Young children in Quebec City had the highest odds of losing a child compared to the Rural West (OR = 2.66, $p < .001$), followed by the GQA (OR = 1.91, $p < .001$) and then the Rural East (OR = 1.50, $p < .05$). Mortality was quite high in Montreal, but many deaths took place in the 2nd quarter or during the first wave of the epidemic. As such, children living in Montreal were not significantly more likely to die in the 3rd and 4th quarters of 1714.

The risk of death during the normal periods was quite different from the risk during the epidemic period. These patterns probably reflect changing mortality conditions over time. In model A, the region of residence was not much of a factor in the risk of death of a child. These patterns are expected because prior to the epidemic mortality conditions did not vary greatly from one region to another. Only Quebec City had a significantly higher odds of losing a child than the Rural West (OR = 1.79, $p < .01$). After the epidemic, conditions worsened in the Western parishes, particularly Montreal, as compared to the East. As such, childhood mortality rates in the West exceeded those in the East, particularly in regards to infant mortality (Mazan et al. 2009). Additionally, the urban/rural mortality differential was now apparent throughout the colony. The high level of urban mortality is reflected in Model C, where both urban towns, Montreal and Quebec City had a higher odds of dying than the Rural West (OR = 1.61, $p < .01$, OR = 2.12, $p < .001$, respectively). In contrast to the epidemic model, children in the Rural East had a significantly lower odds of dying (OR = 0.50, $p < .01$), while children in the GQA were not significantly different from the Rural West.

The age of a child during the epidemic and normal periods was the strongest risk factor in all of the models. In most populations, we would expect to find a rapid decline in the age pattern of mortality between infancy and childhood. This seems to be the case in the normal models, as they follow the typical mortality curve, where the odds of dying rapidly declines from infancy onward (OR = 5.66, 4.71, 4.01 $p < .001$ and OR = 10.17, 5.25, 3.93 $p < .001$, respectively). During the 3rd and 4th quarters of 1714, the mortality pattern was altered to some degree, where the likelihood of dying was highest among young children 12 to 23 months of age. Infants 1 to 6 months old were 4.21 times more likely ($p < .001$), infants 6 to 11 months old were 3.63 times more likely ($p < .001$), while toddlers were 4.87 times more likely to die than children aged 24+ months ($p < .001$). The intensification of the odds ratio at ages 12 to 23 months probably reflects the increased mortality as a result of the measles epidemic. As mentioned above, Measles mortality tends to peak between the ages of 6 and 24 months and declines thereafter (Burstrom et al., 1999). This pattern is clearly evident in Model B to some extent.

Immigrant status of the parents also shows large differences between the epidemic and normal periods. During the epidemic, children with fathers and both parents who were immigrants were at a higher odds of dying, while children of immigrant mothers did not have significantly different mortality than children of Canadian born parents (OR = 1.36, $p < .05$, OR = 2.26, $p < .001$, respectively). In contrast, the immigrant status of parents does not significantly differ from one group to the next during the normal periods. These patterns are consistent in both Models A and C. The sex of the child varies little between the full models fit to the epidemic data and those

fit to the normal data. In all models of under 5 mortality, male children had a higher odds of experiencing a death than female children (OR = 1.32, $p < .05$ vs. OR = 1.43, $p < .01$ and OR = 1.46, $p < .01$ respectively). Although not always the case, female children have been found to have a lower survival rate than males during a severe measles epidemic (Garenne, 1994).

There is some support for the sex differential when estimating these models for children less than 1 year of age and those aged 1 to 4 years (not shown here). In these models, there was an opposite trend between the epidemic and normal models. For the normal models, males under 1 had a higher odds of dying, while the difference for children 1 to 4 years of age was not significant. Conversely, during the epidemic, there was no significant sex difference for infants, while males aged 1 to 4 years had a higher odds of dying than females. These patterns coincide with previous estimations where it was found that female infants were more likely to die from measles, while young male children (1 to 4 years) were the ones more likely to die (Mazan et al., 2009).

Table 4. – GEE and bootstrap logistic regression models comparing mortality of children with and without siblings during the measles epidemic of 1714 and the comparison groups of 1708-10 and 1721-23.

Risk Factor ^a	Model D Normal (1708-10)			Model E Epidemic (1714)			Model F Normal (1721-23)		
	n _{GEE} = 3,083			n _{GEE} = 2,954			n _{GEE} = 3,726		
	n _{BS} = 1,600			n _{BS} = 1,717			n _{BS} = 1,969		
	OR _{GEE}	SE (B)	OR _{BS}	OR _{GEE}	SE (B)	OR _{BS}	OR _{GEE}	SE (B)	OR _{BS}
No. of Siblings									
No Sibs	0.66	0.253	0.58	1.91***	0.175	1.97	0.898	0.193	0.89
1 or 2 Sibs	0.89	0.139	0.93	1.37*	0.142	1.36	1.130	0.124	1.29
3+ Sibs[†]									

[†] Reference category- basis of comparison for the other categories.

p < .001***, p < .01**, p < .05*

^a Controls include: region, age, sex and immigration status.

The number of siblings in the household did not follow the pattern that one would expect, based on other studies. Instead, smaller families or children with 1 or 2 siblings had a higher odds of dying than children with 3 or more siblings (OR = 1.80, $p < .001$). Interestingly, this effect was not present in the normal models. In addition, Model E shows that children with no siblings also had a higher odds of dying than children with 3 or more siblings (refer to Table 4). This effect was even stronger than for children with 1 or 2 siblings (OR = 1.91, $p < .001$ and OR = 1.37, $p < .05$). Possibly, it was the age of the children in the household that was the more important risk factor than the size of the sibship.

The average age difference from the sibship also shows an interesting pattern between the normal and epidemic periods. In the normal models, children who were 6 years and 2 to 5 years apart appear to have had a lower odds of dying, although only children with a 6+ year age difference in the 1708-10 period was significant (OR = 0.63, $p < .05$). During the epidemic, the effect was reversed, where children who were 6+ and 2 to 5 years apart were more likely to die during this period (OR = 1.92, $p < .01$ and OR = 1.48, $p < .05$). In addition, the death of a sibling in the household within the same period also shows an interesting pattern. Although the normal

periods show and increased odds of the death, the death of a sibling was only significant during the 1721-23 comparison group (OR = 1.53, $p < .05$). In the epidemic model, the death of a sibling was highly significant, where a child with a sibling who died would be 4.00 times more likely to die than a child without a sibling who died ($p < .001$). Despite the similar patterns between Models A and C, the highly intensified effect in Model B may be at least partly the result of the measles epidemic.

Table 5. – Bootstrap logistic regression models comparing mortality of opposite and same sex sib-pairs during the measles epidemic of 1714 and the comparison groups of 1708-10 and 1721-23.

Risk Factor	Model G		Model H		Model I	
	Normal (1708-10)		Epidemic (1714)		Normal (1721-23)	
	$n_{BS} = 1,423$		$n_{BS} = 1,497$		$n_{BS} = 1,708$	
	OR _{BS}	SE _{BS}	OR _{BS}	SE _{BS}	OR _{BS}	SE _{BS}
<u>Sib-pair</u>						
Opposite Sex	1.02	0.220	0.90	0.216	0.93	0.205
Same Sex†						
<u>Age Difference</u>						
6+ years	0.85	0.266	1.90*	0.276	0.82	0.243
2 to 5 years	0.89	0.345	1.36	0.342	0.85	0.336
< 2 years†						

†Reference category- basis of comparison for the other categories.
 $p < .001^{***}$, $p < .01^{**}$, $p < .05^*$

A simple way to test whether the sex of siblings is a mortality risk during the epidemic is to examine sibling-pairs. I replicated (to some extent) Pison et al. study on Senegal to examine the possibility of cross-sex transmission during the measles epidemic. I randomly selected sib-pairs less than 10 years of age and then randomly selected one of the pairs for the analysis. This random selection procedure was repeated 100 times with replacement. The same controls were used to test for the effects of cross-sex transmission between the child and one of their siblings during the epidemic and normal periods (refer to Table 4). Models D through F show the bootstrapped odds ratios and standard errors of the coefficients for the sib-pair analysis. There appears to be no evidence of cross-sex transmission during the epidemic. The odd ratios show that the risk of death was similar for opposite and same sex siblings. In addition, the models were also run using households with two children at the time of the epidemic and normal periods (similar to Pison et al., 1992). No significant differences were found in these models, as well (not shown here). However, consistent with Model B, the age difference between the sibling-pairs was significant. In this model, however, only children who were 6 or more years apart from their designated sibling-pair was significant (OR = 1.90, $p < .05$).

Discussion

This study was a first step in exploring whether one can find similar patterns in disease processes between historical and modern populations. A limitation of the Quebec data was that parish clergy did not record the cause of death at the time. To alleviate this problem, to some extent, I applied stringent selection criteria and a crude method that consisted of comparing a risk model

applied to the epidemic data with the same model applied to data from normal periods (i.e. a form of validation). Although there was no way to distinguish between measles and non-measles deaths, these methods helped to identify the possible role that demographic and familial risk factors played during the measles epidemic. As a result, many tentative ideas about the disease process were generated and I was able to find some general similarities and differences with historical and modern studies conducted in other populations.

Methodologically, this study has shown the importance of validation and knowing the historical situation of a study population. Validation can help to identify peculiarities and patterns in the data that would not be possible analyzing only a single period. In other words, it helps to identify period disturbances that may alter the results of the statistical models. Additionally, knowing the historical situation of the population will enable one to make more valid conclusions about the applicability of the models applied to the data. Simply, ignoring one or the other of these issues may lead to erroneous conclusions about the findings of a study.

The regional differences during the epidemic replicated the aggregate results from a previous study on the demography of the epidemic (Mazan et al. 2009). Children in the Eastern parishes were at a much higher risk of death than children in the West. This was particularly true in Quebec City and the rural parishes surrounding the urban town (GQA). We suspected that poor harvests reported between 1714 and 1717 played a role in the regional mortality differences (Crowley, 1991). Although there was no indication of the exact regions affected or whether the entire colony experienced poor harvests, we suspected that the inadequate harvests were largely confined to the East and may have played role in making these children more susceptible to death from infection. Malnutrition is regarded as a major predictor of measles mortality. It is believed that the influence of malnutrition is mediated through immune suppression (Clements and Hussey, 2004). In particular, vitamin A deficiency and protein energy malnutrition are the common nutritional risk factors associated with an increased risk of death from measles.

In some studies, female children have been found have a higher probability of death from measles (Garenne, 1994). In this study, sex differences were not so clear between the epidemic and normal periods for children under 5 years of age. In all of the models, males were at a higher risk of death than females. These findings do not mean that females were not at a higher risk of death. Rather, the sex difference may come into effect depending on the age of the child. When I estimated models for different age groups (i.e. children less than 1 year of age and those aged 1 to 4 years) there was an opposite trend between the epidemic and normal models. In the normal models, males under 1 had a higher odds of dying, while there was no significant sex difference for children 1 to 4 years of age. Conversely, during the epidemic, there was no significant sex difference for infants, while males aged 1 to 4 years had a higher odds of dying than females (not shown here). These patterns coincide with previous estimates where it was found that female infants were more likely to die from measles, while young male children (1 to 4 years) were the ones more likely to die. In the previous study, the largest sex difference was found in older children aged 5 to 14 years, where females were estimated to have a higher risk of measles death.

Several community studies on Africa, Asia and Europe found that mortality was higher in families with several cases and among secondary cases (i.e. children infected at home). In these studies, the 'effect of malnutrition was less important than overcrowding and intensive exposure

to the virus' (Garenne and Aaby, 1989; Aaby, 1984; 1988). In this study, there was no evidence that larger sibships led to an increased risk of death. To the contrary, it was found that children in smaller sibships consisting of 1 or 2 children had a higher risk of dying. Further, children with no siblings also had a higher risk of death than larger sibships. In modern populations, large families tend to be poorer and less educated, as lower socioeconomic status has also been found to be associated with an increased risk of measles death (Burstrom et al., 1999).

In historical Quebec, however, a large family may have indicated greater wealth than smaller young families just starting their reproductive lives. Larger families would imply that there was greater access to resources and probably to more fertile lands, since many had been established for generations. If there were poor harvests, these larger families may have been better off because of mutual support from an extended kinship. The family was considered a 'collective and egalitarian unit' and its members tended to migrate together and establish farms within a close proximity (Bouchard, 1994). Bouchard (1992) indicates that sons emigrated to settle newly opened land and the family helped with the initial clearing. As *pionniers accapareurs* ("monopolizing pioneers"), siblings would cooperate to take over large stretches of land to establish themselves and their descendants (Mathieu et al., 1992; Gagnon, 2001). This characteristic allowed family members to remain close to one another.

These aspects may help to explain why children with immigrant fathers and both parents were at a higher risk of death, while ones with mothers who were immigrants had no different mortality from children of Canadian born parents. It is possible that children with fathers and both parents who were immigrants may have lacked support from an extended kinship during crises such as, poor harvests and an impending epidemic. Large well established Canadian families may have acted as a buffer against crises such as food shortages by helping one another (i.e. access to abundant resources), while immigrant parents may have had little help during a crisis situation. However, it would not matter so much if the mother was an immigrant because their Canadian born husband may have been more likely to belong to a well established family. These attributes may have helped children remain adequately nourished and have a better chance of fighting off the infection.

This by no means implies that there is no sibling effect on the risk of death during the epidemic. When a sibling died, the risk of death of the child was greatly intensified during the epidemic period. Although there is no direct way to distinguish between index and secondary cases, the death of a sibling may reflect the incidence of multiple and secondary cases in a given family. When there are multiple and secondary measles cases in a family, the risk of death is increased greatly for those particular cases. Generally, it is suggested that close contact with other family members increases the generational intensity of the virus. The increased mortality risk associated with close family contact is the 'dose-response effect', where a higher dose of the virus is transmitted to other family members (Garenne and Aaby, 1989). As such, this implies that the sibling effect on the risk of death may be mediated through intensive exposure to the virus.

In all studies, the age at infection has also been found to be an important risk factor of measles mortality (Reves, 1985; Pison et al., 1992; Burstrom et al., 1999). As mentioned above, deaths from measles usually peak between the ages of 6 and 24 months and declines thereafter (Burstrom et al., 1999). In New France, the age pattern of mortality was the strongest risk factor

and followed this trend during the epidemic, where 1 to 2 year olds were at the highest risk of dying. During the normal periods, mortality showed a typical mortality pattern, where the likelihood of dying rapidly declined from infancy onward. In another study, the age difference between siblings pairs and cross-sex transmission increased the risk of dying (Pison et al., 1992 and Aaby, 1992). No support was found for the increased mortality between sibling pairs of the opposite sex, but a larger age difference between siblings resulted in a higher odds of death from measles.

In the case of Quebec, older children may have been more likely to be infected outside of the home (index child) and then infect the younger children in the household (secondary cases). Older children would have a better chance of fighting off the infection because of a weaker dose and a fully developed immune system. Younger children, on the other hand, would be at a dual disadvantage because of an underdeveloped immune system and further suppression due to widespread malnutrition. In turn, younger children who contracted the virus, given the age-associated differences in risk and the intensity hypothesis, would have a greater likelihood of dying (Reves, 1985; Pison et al., 1992; Burstrom et al., 1999). In addition, it is quite possible that the parents could have been the index case, especially for children with no siblings. This same disease process could apply in these situations, as well.

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